



**Conclusions:** A regular dose of C increases WR. A second dose consumed shortly after produces a smaller but discernible adverse effect on WR adding up to a prolonged total effect. This finding has important implications for arterial stiffening and the pulsatile load of the heart and may be involved in the pathogenesis of hypertension.

1133-118

#### Changes in Left Ventricular Structure and Function Predict the Onset of Hypertension in Adult Normotensives With a Family History of Hypertensive Disease: A Seven-Year Follow-Up Study

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**Background:** Alterations in left ventricular (LV) structure and function have been previously shown in normotensive offspring of hypertensive (HT) families but their significance is still unclear.

**Methods:** To verify if these alterations have predictive value for the onset of HT disease, 205 normotensive adults (mean age 43±10 yrs) with family history of HT, were examined echocardiographically (2D, M mode, Doppler) at baseline and then repeatedly at 12 months intervals, during a follow-up period of 7.1 yrs (range 4-7.5 yrs).

**Results:** During this period, 57 subjects (28%) became hypertensive (H group). These subjects had higher values for the baseline LV mass index (LVMI) (97 ± 25 g/m<sup>2</sup> vs 81 ± 21 g/m<sup>2</sup>; p<0.01), lower age adjusted E/A ratios (1.1 ± 0.4 vs 1.4 ± 0.4; p<0.001), and lower LV longitudinal fractional shortening (0.16 ± 0.03 vs 0.19 ± 0.03; p=0.038) compared to those who did not develop HT (N group). The subjects in the H group had also higher initial systolic blood pressure (SBP) (134 ± 12 mmHg vs 117 ± 11 mmHg; p<0.01) and a higher number of 1st degree relatives with HT (2.9 ± 0.3 vs 1.5 ± 0.4; p=0.044).

There was no significant difference in baseline LVEF, LV circumferential fractional shortening, LV end diastolic diameter and left atrial size between H and N subjects at baseline.

SBP at the end of the follow-up was predicted independently by the initial SBP (beta=0.359; p<0.01), age (beta 0.01, p=0.042) and LVMI (beta=0.185; p<0.01).

During the follow-up period, the subjects who subsequently developed HTN, experienced a significant increase in LVMI (from 97±25 g/m<sup>2</sup> to 104 ± 26 g/m<sup>2</sup>; p=0.039), and increase in aortic diameter (from 32 ± 4 mm to 36 ± 6 mm; p<0.01). The paired differences for all these parameters were significantly higher in the H group compared to the N group. H subjects had also higher variations in LV-E/A between the echo exams in the follow-up period when compared to the N group (coeff var 25% vs 12%; p<0.01).

**Conclusions:** Increased LV mass and alterations in LV diastolic and systolic longitudinal function predict the onset of HT in normotensives with family history of HT. Increased variability in LV diastolic function seem to appear during the period of developing HT.

1133-119

#### N-Terminal Pro-Brain Natriuretic Peptide Predicts Cardiovascular Events in Hypertension: A LIFE Substudy

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**Background:** N-terminal pro brain natriuretic peptide (NT-proBNP) is a strong cardiovascular risk factor in patients with chronic heart failure as well as in the general population. We wanted to investigate whether high NT-proBNP could predict the composite endpoint (CEP) of cardiovascular death, non-fatal stroke or non-fatal myocardial infarction in patients with hypertension and left ventricular hypertrophy as well. **Methods:** After two weeks of placebo treatment and yearly for 4-5 years clinical, laboratory, and echocardiographic variables were assessed in 184 hypertensive patients from the LIFE Echo substudy, aged 55-80 (mean 66±7) years, with electrocardiographic LV hypertrophy. NT-proBNP was measured by immunoassay (Elecys proBNP) at baseline and after one year of treatment.

**Results:** CEP occurred in 25 patients. Baseline NT-proBNP above the median value of 185 pg/ml was associated with higher incidence of CEP (18.7% vs 8.7%, P<0.05). Known cardiovascular disease (n=60) defined as diabetes (n=20), or history of either ischemic heart disease (n=26), cerebrovascular disease (n=19), peripheral vascular disease (n=5) or chronic heart failure (n=2), was also associated with higher incidence of CEP (24.6% vs. 8.9%, P<0.01). NT-proBNP above the median value was not associated with higher incidence of CEP in this high-risk group (24.3% vs. 21.7%, NS), but was in the remaining 124 "low-risk" hypertensive patients (14.8% vs. 4.3%, P=0.01). In Cox regression analyses controlling for treatment assignment NT-proBNP (P<0.05) predicted CEP slightly more strongly than prior cardiovascular disease (P=0.054) and current/prior smoking (P=0.06). Systolic blood pressure, gender and body mass index did not enter the model. NT-proBNP levels after one year of treatment also tended to predict the CEPs

that occurred subsequently (18.6% vs. 9.2%, P=0.07). **Conclusion:** NT-proBNP is a strong cardiovascular risk factor in patients with hypertension and LV hypertrophy, especially in the group without diabetes or clinically overt cardiovascular disease. Furthermore, our data suggest the possible use of NT-proBNP - even measured during treatment - as a practical tool for risk stratification in hypertension.

1133-146

#### Genetic Analysis of Multiple Risk Factor Syndrome in Rats

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**Background:** According to epidemiological studies, cardiovascular risk factors tend to cluster in certain individuals, which has been widely recognized as the multiple risk factor syndrome. To clarify pathophysiological mechanisms underlying the multiple risk factor syndrome, we performed extensive genetic analysis using a unique model organism, the spontaneously hypertensive rat (SHR).

**Methods:** We undertook genome-wide screens in 2 F2 cohorts independently produced from the Wistar-Kyoto rat and SHR of a Japanese colony (151 males in F2-1 and 175 males in F2-2). In addition to blood pressure, plasma lipid, glucose and insulin levels, and body weight, in vitro phenotypes associated with insulin resistance and fat pad weight were evaluated in F2-1, while part of F2-2 (n=32) were fed high-fat-high-cholesterol (HFHC) diet between 15 and 17 weeks of age.

**Results:** In the entire progeny, the most significant linkage to blood pressure was found near D3Mit14 on rat chromosome 3 (maximal LOD score=5.0), where linkage to triglyceride levels was concomitantly observed. Also, suggestive linkage was observed for blood pressure and cholesterol levels on rat chromosome 19. Significant linkage to body weight was observed near D2Mit5 on rat chromosome 2 (maximal LOD score=4.0 in F2-2). There was a suggestive evidence of linkage to in vitro phenotypes, i.e., glucose uptake and lipolysis measured in isolated adipocytes, in a region between D4Mgh17 and D4Mgh11 on rat chromosome 4, far distant from the Cd36 locus. In several chromosomal regions, statistical significance of linkage was enhanced after HFHC diet.

**Conclusion:** We have identified the clustering of linkages to more than 1 phenotypic traits on a few chromosomes, suggesting the potential existence of genes controlling multiple cardiovascular risk factors at least in rats. Our data also provide a substantial evidence for a gene-environment interaction, that is, some quantitative trait loci become prominent after a certain dietary intervention. Further investigation including the development of congenic strains is currently in progress to resolve these issues.

1133-147

#### Cardiovascular Morbidity and Mortality in Hypertensive Patients With Atrial Fibrillation: The LIFE Study

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**Background:** Optimal treatment of hypertensive patients with atrial fibrillation (AF) to reduce the risk of cardiovascular morbidity and mortality remains unclear.

**Methods:** As part of the LIFE study, 324 patients (42% women) with AF and hypertension (mean age 70±6, pressure 176±14/96±10 mmHg) and electrocardiographic left ventricular (LV) hypertrophy, were assigned to losartan- or atenolol-based therapy for 1,385 patient-years of follow-up.

**Results:** The primary composite endpoint occurred in 36 patients in the losartan-group (n=150) vs. 64 in the atenolol-group (n=174); relative risk (RR) 0.60 [95% CI 0.40-0.92], P=0.018. Cardiovascular deaths occurred in 20 vs. 37 patients in the losartan- and atenolol-group, respectively; RR 0.58 [CI 0.34-1.01], P=0.053. Stroke occurred in 18 vs. 37 patients (RR 0.56 [CI 0.31-0.97], P=0.040), and myocardial infarction in 11 vs. 7 patients (P=NS). There was a trend towards lower all-cause mortality; 30 vs. 48 (RR 0.67 [CI 0.43-1.07], P=0.092), and hospitalization for heart failure took place in 15 vs. 23 patients (P=NS). Adjustment for blood pressure levels during follow-up had little impact on cardiovascular benefit of losartan.

**Conclusion:** Losartan was more effective than atenolol-based therapy in reducing the risk of the primary composite endpoint of cardiovascular morbidity and mortality, as well as the secondary endpoints of stroke and cardiovascular death, in hypertensive patients with electrocardiographic LV hypertrophy and AF and there was a trend towards lower all-cause mortality. Hypertensive patients with electrocardiographic LV hypertrophy and AF seem to benefit more, for the same blood pressure lowering, from losartan than from conventional antihypertensive and antiarrhythmic treatment by atenolol.

1133-148

#### Cardiovascular Safety of Vardenafil in Patients Receiving Antihypertensive Medications: A Post-Hoc Analysis of Five Placebo-Controlled Clinical Trials

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**Background:** Hypertension is associated with erectile dysfunction (ED). Phosphodiesterase 5 (PDE-5) inhibitors may potentiate blood pressure (BP) reduction of antihypertensive agents (HTM). This study evaluated the cardiovascular safety of vardenafil, a potent, selective PDE-5 inhibitor when used with HTM.

**Methods:** Data were extracted from 5 double-blind Phase III trials in which 2,718 men with ED received vardenafil 5, 10, or 20 mg or placebo as needed for up to 26 weeks. Adverse events and vital signs were tabulated at all visits; in a patient subgroup (n=703), vital signs were recorded 11 min to 5 h post-dose. Vardenafil doses were pooled and analyzed by HTM use.

**Results:** In 2,605 patients valid for safety (varidenafil-1,812, placebo-793), ≥1 HTM was